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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

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COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to ~~communication(s)~~ application filed on 3/3/95

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-32 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-32 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

2. The Abstract of the Disclosure is objected to because of the word "new" at line 10. The abstract should not refer to purported merits. The Abstract of the Disclosure is objected to because of the word "disclosed" at line 1. The abstract should avoid legal phraseology. Correction is required. See MPEP 609.01(b).

3. The disclosure is objected to because of the following informalities:

a. page 1, line 19, change "ingestible of orally" to "ingestible, orally" or to whatever applicants deem appropriate to correct the grammatical error

b. page 2, line 5, change "of extracellular matrix" to "of the extracellular matrix"

c. page 4, line 13, change "offers" to "offer"

d. page 13, line 15, change "tether" to "tethers"

e. page 13, lines 21 - 22, change "ensure a" to "ensures that a"

f. page 20, line 10, for the phrase "following non-limiting" it appears that applicants may have intended to say "following non-limiting examples"

g. page 23, line 12, change "reprecipitated" to "re-precipitated"

Appropriate correction is required.

4. The drawings are objected to because in Figure 2 the word "coupled" appears to mean "tethered"; the latter term is used throughout the disclosure and in the claims, and it is recommended that applicants change the term "coupled" to "tethered" so as to remain consistent. Correction is required.

5. Applicant is required to submit a proposed drawing correction in response to this Office Action. Any proposal by the applicant for amendment of the drawings to cure defects must consist of two parts:

a) A *separate* letter to the Draftsman in accordance with MPEP § 608.02(r); and

b) A print or pen-and-ink sketch showing changes in *red ink* in accordance with MPEP § 608.02(v).

IMPORTANT NOTE: The filing of new formal drawings to correct the noted defect may be deferred until the application is allowed by the examiner, but the print or pen-and-ink sketch with proposed corrections shown in red ink is required in response to this Office Action, and *may not be deferred*.

6. Claims 5, 6, 9, 25, 29 and 30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

For Claim 5, line 2, change "consisting synthetic" to "consisting of synthetic" so that proper Markush language is used

For Claim 6, lines 3 - 4, the semicolons should be changed to commas

For Claim 9, line 6, a comma should be inserted after "proteins"

For Claim 25, line 6, a comma should be inserted after "proteins"

For Claim 29, line 1, "form" should be changed to "from"

For Claim 30, this claim is dependent upon a rejected claim

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 - 9, 13, 19 - 26 and 31 are rejected under 35 U.S.C. § 102 b as being anticipated by Clapper et al. Clapper et al. disclose a cell culture support consisting of a support material, a positively-charged molecule and a cell adhesion

factor (see claim 7 . It is disclosed that "the positively-charged molecule and the cell adhesion factor are covalently bound to one another and either the positively-charged molecule or the cell adhesion factor is covalently bound to the supporting surface" (see claim 7 (b)). Clapper et al. disclose that the support material can be prepared from many materials including synthetic polymers (see column 5, line 36 - 50), zirconia, alumina, glass and silica (see column 5, lines 52 - 53). It is disclosed that this cell culture support can be "in any suitable form, for instance, as membranes, tubes, microtiter wells, columns, hollow fibers, roller bottles, plates, dishes, and solid, hollow, or porous beads" (see column 5, lines 55 - 58). It is disclosed that the positively-charged molecule are synthetic (see column 7, line 44) and include carboxy methyl cellulose (see column 7, line 67). Clapper et al. disclose that the cell adhesion molecule include the extracellular matrix molecules "laminin, fibronectin, collagens (all types), vitronectin, and tenascin" (see column 6, lines 40 - 41). Clapper et al. disclose that this cell culture support can be used for "cell culture of mammalian cells" (see column 1, line 21 .

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section

> 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 1 - 9, 13 - 16, 18 - 25 and 31 are rejected under 35 U.S.C. § 103 as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264). Herweck et al. disclose a device which can be used for stimulating the growth of eukaryotic blood cells see Abstract and column 11, lines 24 - 49 and using this device as a "matrix and support upon which cellular matter is grown" column 11, lines 26 - 27 . This device consists of a substrate which can be manufactured from any suitable biocompatible material including fibers and polymers see column 8, lines 44 - 57 . Herweck et al. disclose that the substrate of the device can be shaped in any way needed for its required

application (see column 4, lines 21 - 25). This device is also disclosed to be implantable (Abstract, line 1) and useful for treating a patient in need of cell growth (column 4, lines 39 - 40 and claim 29). Herweck et al. also disclose coating the substrate of the device with bioactive material such as platelet derived growth factor, epidermal growth factor, transforming growth factor, erythropoietin, and fibroblast growth factor (see claim 25 and column 12, lines 1 - 35). Herweck et al. do not disclose biocompatible tethers which have one end covalently linked to the substrate and a growth effector molecule covalently linked to the other end. Merrill discloses star molecules composed of biocompatible, non-thrombogenic, water-soluble polyethylene oxide (PEO)(see Abstract and column 1, line 21) which can have one arm covalently linked to a substrate thereby anchoring the molecule (see column 2, lines 11 - 14) and another arm covalently linked to a bioactive molecule (see column 5, lines 3 - 9 and claim 15). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a composition for use in stimulating the growth of eukaryotic blood cells consisting of a biocompatible substrate, biocompatible tethers and growth effector molecules as described by Herweck et al. using the polyethylene oxide star molecules for the biocompatible tether components as described by Merrill because the star molecules will prevent thrombogenesis from occurring when the device of Herweck et al. is implanted while

still ensuring that the device remains coated with the bioactive material.

11. Claims 10 - 12 and 26 - 28 are rejected under 35 U.S.C. § 103 as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 19 - 25 and 31 above and further in view of Merrill (J. Biomatter Sci. Polymer). Merrill discloses that the "length of each PEO chain corresponds to its molecular weight and typically range from about 1,000 to about 10,000" (see column 2, lines 56 - 58). Merrill (J. Biomatter Sci. Polymer) discloses that the arms of PEO consist of varying numbers of ethylene oxide monomers (CH_2OCH_2) (see page 3). The molecular weight of one of these monomers is 44 daltons. Therefore, a PEO chain of 1,000 daltons would correspond to approximately 23 monomers corresponding to approximately 68 backbone atoms and a PEO chain of 10,000 daltons would correspond to approximately 680 backbone atoms. Therefore, it would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to design a composition for stimulating the growth of eukaryotic cells as described above and choosing a PEO chain length such that the backbone of the tether i.e. from substrate to growth effector molecule would include 2 PEO chains and the central divinyl benzene molecule which is 8 atoms could vary in length between about 136 and 1361 atoms as suggested by Merrill J.

Biomatter Sci. Polymer ; optimization within this range would have been obvious to one of ordinary skill in the art at the time applicants' invention was made because Merrill '764 discloses chain length to be a result-effective variable.

12. Claims 10 - 12 and 26 - 28 are rejected under 35 U.S.C. § 103 as being unpatentable over Clapper et al. Application of Clapper et al is the same as in the above rejection of claims 1-9, 13, 18-25, and 31. Clapper et al. disclose polymers as the positively charged molecules, but do not disclose backbone length of the polymers. It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to determine all operable and optimal backbone lengths for the positively charged molecules of Clapper et al. because degree of polymerization, i.e. backbone length, is an art-recognized, result-effective variable which is routinely determined and optimized in any art involving polymers

13. Claim 17 is rejected under 35 U.S.C. § 103 as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Mikos. Neither Herweck et al. nor Merrill disclose a substrate which is biodegradable. Mikos discloses a "biodegradable, bioresorbable , three-dimensional template for repair and replacement of diseased or injured bone

which provides mechanical strength to bone while also providing a guide for growth of bone tissue" (see Abstract, lines 1 - 4). Mikos discloses that "the implant is seeded with osteoblasts prior to implantation to provide regeneration sites for bone tissue" (see column 1, lines 64 - 68). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a cell growth composition outlined in the above rejection using a biodegradable material as described by Mikos because a patient in need of an implantable cell growth composition might only need it for a defined period of time and it would be less deleterious to the patient and more conducive to overall healing to have the cell growth composition biodegrade and be bioabsorbed so that further surgery and trauma to the patient would not be necessary.

14. Claims 29 and 32 are rejected under 35 U.S.C. § 103 as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Naughton et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for parenchymal or stem cells. Additionally, neither Herweck et al. nor Merrill disclose using a cell growth composition for testing a compound for its effect on tissue. Naughton et al. disclose a "three-dimensional cell culture system which can be used to culture a variety of different cell" (see Abstract, lines 1 - 3).

It is disclosed that this system can be used to culture parenchymal cells and stem cells (see column 13, last paragraph continuing to column 14). Naughton et al. also disclose using this system in cytotoxicity assays (see column 1, line 33 - 34). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to use the cell growth composition outlined in the above rejection to culture parenchymal and stem cells and to perform cytotoxicity assays, both as described by Naughton et al., because different cell culture methods are routinely sought in the cell culture art and because *in vitro* drug testing methods are preferable to *in vivo* drug testing methods so that animals are not harmed and cost is contained.

15. Claims 29 and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 19 - 28 and 31 above, further in view of Tomomura et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for hepatocytes. Tomomura et al. disclose that "rat hepatocytes in primary cultures lack the ability to proliferate" (Introduction, paragraph 1, lines 5 - 6) and that cultured rat hepatocytes are stimulated to replicate by addition of epidermal growth factor (see Abstract). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to

use the cell growth composition outlined in the above rejection with epidermal growth factor as the growth effector molecule for cell culture of hepatocytes because such a cell culture would be useful because the liver is the "detoxification center" of the body, however, when acting upon a compound, the liver may convert it to a form which is also toxic or in some way deleterious to the organism, so it would be useful to have long term cultures of hepatocytes to use for *in vitro* biotransformation reactions of chemicals, the biotransformation products of which could then be tested *in vitro* on other cultured cell types.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen Carroll, Ph.D. whose telephone number is (703) 305-7122. The examiner can normally be reached on Monday through Friday from 8:30 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Elizabeth Weimar, can be reached on (703) 308-0254. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

KC

Kathleen Carroll, Ph.D.
August 13, 1996

JEFFREY E. RUSSEL
PRIMARY PATENT EXAMINER
ART UNIT 1815